inhale

March 16, 1999

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Dockets Management Branch, HFD-305
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Dear FDA Colleague,

Attached are comments from Inhale Therapeutic Systems on the Draft Guidance for Industry for Metered Dose Inhalers (MDI) and Dry Powder Inhale (DPI) Drug Products, Chemistry, Manufacturing, and Controls Documentation, docket number 98D-0997. We greatly appreciate the Agency's flexibility in allowing extra time to review and comment (as discussed via telephone on 2/16/99 by Ms. Joan Powers, FDA Drug Information Branch, HFD-210 and Dr. Lynn Van Campen, Inhale), and trust you will find our proposals useful.

We look forward to working with FDA to advance the state of knowledge of pulmonary drug delivery, especially with regards to using deep lung delivery as a means of systemic drug delivery.

Please call me ((650) 631-3177) if I can be of assistance or if you have any questions or comments regarding this correspondence.

Sincerely,

Michael A. Eldon, Ph.D., F.C.P.
Director, Regulatory Affairs

Attachment

98D-0997

C25

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Comments on

FDA Guidance for Industry: Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products

submitted by

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San Carlos, California 94070
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Overview

Inhale Therapeutic Systems develops dry powder pulmonary delivery systems principally directed toward systemic delivery of macromolecule drugs through the deep lung. Accordingly, there are several key attributes that distinguish Inhale's delivery system from currently marketed DPIs, and which qualify the applicability of portions of this guidance: (1) patients using this delivery system generally have normal lung function; (2) the dispersion and aerosolization of the pre-metered dose occur separately and independently from patient inhalation; and (3) our aerosol powders are manufactured using spray drying, resulting in all particles having the same composition. Otherwise the DPI category of this guidance appears generally appropriate.

In general the guidance provides a perspective on the uniqueness of the inhalation route for drug delivery and specific CMC activities that are expected to be conducted to characterize a pulmonary delivery system and drug product. The information in this document has generally been expected based on previous FDA guidance and feedback provided to Inhale. It provides clarity of the FDA's expectations in some areas, especially with regard to characterization of both MDI and existing DPI dosage forms.

While the information and clarification in the guidance is appreciated, it appears applicable primarily to MDIs and DPIs used for local delivery of drugs to the lungs such as in the treatment of asthma. Based on our experience, we believe that the guidance will not adequately cover a variety of issues raised in the development of a pulmonary delivery system intended to result in substantial and reproducible systemic drug absorption. Because of this, Inhale reserves the right to comment further as our experience with systemic delivery of molecules such as insulin increases. In that light, we are pleased to provide the Agency with the following comments.

General Comments

The Agency suggests in the Introduction that "the recommendations in this guidance should also be considered for INDs." Inasmuch as safety concerns predominate at the

IND stage of product development documentation and support, it is expected that issues of safety will largely distinguish between CMC documentation needed for IND submission and that required to support final product registration (NDA or BLA).

As drug molecules targeted for systemic therapy are becoming candidates for inhalation delivery, the guidance document should also reflect this application. Specifically, reference to the use of a particular patient population with diseased lungs should not be required when the goal is to provide systemic drug delivery to patients with healthy lungs. It is recommended that the choice of "an appropriate patient population" replace any specific reference to COPD or asthma patients.

Additionally, this guidance document should be used in conjunction with other relevant regulatory guidance wherever possible so as to minimize inconsistent regulatory expectations. For example ICH Guidelines should be referenced, as well as other FDA Guidance documents (e.g.., Submission of Documentation in Drug Applications for Container Closure Systems Used for the Packaging of Human Drugs and Biologics, June 1997).

The guidance as written covers recommendations for MDIs and existing DPIs. There are a number of unit dose and multidose liquid aerosol devices under development. For example, the Respimat device is being developed by Boehringer Ingelheim for the delivery of asthma medications, and the AERx device is being developed by Aradigm for morphine and inhaled insulin. These devices do not currently seem to be covered by the guidance on nebulizer preparation and yet are not covered in this proposed guidance either. While it is appreciated that these devices have not yet reached the NDA review stage, it is recommended that the appropriate additions be made to include them in this guidance since most of the issues addressed here are relevant to these liquid systems as well.

Specific Comments

Lines 64 and 143
Recommend rewording of these sections to reflect the possibility of successfully completing bioequivalence studies for pulmonary delivery systems that achieve substantial systemic delivery. The section starting with Line 64 should be made specific for MDIs rather than for "oral inhalation aerosols" in general, whereas the section starting with Line 143 should be modified to indicate that bioequivalence studies may be possible under certain conditions.

Line 137-138
The statement on electrostatic charge should be reworded to generalize the effects of electrostatic forces on the efficiency of DPIs.

Line 171-225
The same requirements should be reflected for both MDI and DPI quantitative composition in terms of the metered or emitted dose. Line 195 relates to the "amount of active ingredient per actuation from the mouthpiece" for MDIs, whereas lines 216-220 relates to the amount of "each active and excipient..... per metered dose and emitted dose at the mouthpiece" for DPIs.

Line 235-245
This statement pertains to the physical properties of the drug substance, where this material will be used in this form without modification, other than size reduction. These requirements for characterization are not appropriate where this physical form of the drug substance is not relevant to the final product, for example, when the drug substance is dissolved as part of the manufacturing process.

Line 246-257
Recommend a reference to the relevant guidance document on impurities. This will prevent any misinterpretation of the various documents that relate to impurity profiling and qualification and will maintain consistency in the case that one or more of the documents may undergo further revision.

Line 265-267
Recommend rewording of this statement, as some products will not be targeted at patients with sensitized airways.

Line 414.
Recommend that this section be revised to recognize that there are forms of processing other than micronization that are used to control the primary particle size of the drug product, e.g. spray drying.

Line 449-451
Recommend removal of specific reference to "for seal completeness and for seal strength" to allow for integrity tests appropriate to individual drug products.

Line 624-626
For certain DPIs the nominal dose is controlled during filling to target unit dose fill weights. For these pre-metered dose systems, mass balance can only be accurately calculated in reference to emitted dose.

Line 743
Recommend replacing "strictly limited" with "controlled," as moisture content may not necessarily be best limited to a minimum level. Moisture levels should be controlled, however, dependent upon individual product performance and stability.

Line 757
This reference to the relevant MDI section should also include a reference to the relevant ICH guidance on drug products.

Line 764
Recommend that the volume of air drawn through the device for dose content uniformity be limited to "no more than two liters."

Line 758
The reference in the DPI section for Dose Content Uniformity back to the MDI section relates to testing on multiple containers. A statement to allow the testing to be performed on appropriate individual unit dose packs should be included. Separate testing appropriate for the delivery system or device, should obviate the need to use multiple devices for this test, especially for re-usable pre-metered dose delivery systems.

Line 803
The Container and Closure System section should refer, where possible, to the previous FDA Guidance (Draft) issued June 1997. The section relating to the extraction studies, in particular, is not in agreement with other relevant guidance. This is especially true where the food additive or contact regulations are cited.

Lines 1101 - 1104
Recommend changing this statement to differentiate the DPI device from the blister-packed formulation, i.e.: "As with MDIs, the clinical efficacy of the DPI drug product may be directly dependent on the design, reproducibility, and performance of the container and closure system. When the drug dosage is stored within the device, the DPI container and closure system consists of the overall device and the primary and protective packaging (e.g., overwrap). When the DPI consists of a device and a separate container closure system for pre-metered unit doses, the container closure system for the dosage shall be governed by the applicable guidelines that are listed in the Guidance for Industry for Container Closure Systems Used for the Packaging of Human Drugs and Biologics. The design, composition, and quality control of the individual components of the container and closure are key to maintaining the chemical and physical stability of the...."

Line 1106
For a pre-metered and re-usable DPI, the primary drug container/closure alone (e.g. blister pack) defines the shelf stability of the product prior to use. The device itself is key to ensuring performance of the delivered drug product.

Lines 1133 & 1191
Air flow resistance for devices that do not rely on patient effort to deagglomerate the powder drug substance may not be a relevant performance parameter. Inhale agrees that supportive data should be included to illustrate this characteristic.

Line 1159
Critical mechanical components that may affect the mechanics of the overall performance of the device should be properly specified and tested. However, they should not be required to meet extractives testing levels that apply to materials that are in direct contact with the drug substance (such as the primary drug packaging), or are in intimate contact with the patient (such as the mouthpiece).

Lines 1166-81
The levels of quantitation (0.5 ppb) called for in the assessment of extractives for food contact/additives are unlikely to be achieved. If a reasonable level of identification and quantitation can be performed to establish a baseline, and appropriate biocompatibility tests are performed on said lots of material, then sufficient grounds should have been presented to establish safety and to support indirect monitoring of subsequent lots.

Line 1170
Add to end paragraph: "Components that come in transient contact with the dry powder should meet USP Physicochemical Test criteria for plastics (USP <661>) and USP Biological Reactivity Test criteria (USP <87> and <88>)."

Lines 1175 - 1177
Recommend changing statement to: "Safety concerns for the device will usually be satisfied if the components that come into contact with the patient (such as the mouthpiece) or with the drug meet USP Biological Reactivity Test criteria (USP <87> and <88>).

Lines 1184 - 1187
Recommend changing this statement to: "Based on the analytical and toxicological evaluation of the extractables from the control extraction study, the applicant should establish discriminatory test methods and set appropriate criteria for the extractable profile(s) for routine testing of incoming individual critical components (e.g., mouthpiece)."

Line 1209
The requirement for drug product stability testing at 25°C/75%RH in its protective overwrap for at least one third of the shelf life is questioned if no significant change for 6 months at 40°C/75%RH has been observed. Additionally it is noted that this new stability condition is not included in the ICH stability guidelines.

Line 1251
It is recommended that accelerated stability testing be carried to 6 months for ANDA products as well.

Line 1578
Recommend that the volume of air drawn through the device for dose content uniformity be limited to "no more than two liters."

Line 1580-1588
This section relates to studies in patients with diseased lungs. Some DPIs are not targeted to be used in patients with diseased lungs, and therefore the following change is recommended to this section from line 1582: "....and dose delivery), studies should be conducted in the relevant patient populations."

Line 1581
Not all DPI devices depend on patient effort for deaggregation and delivery. We agree, however, that studies should be done to assess and demonstrate the effects of flow rate on emitted dose, and where practical, particle size. These studies should be performed at constant and realistically small volumes.

Line 1600-1602
Recommend that this last sentence be moved to the section relating to "Effect of Patient Use."

Line 1606
Recommend replacing "proportionality" with "relationship."

Line 1613
Propose to assess the "microbial limits" before a new device is put into service by the patient, and then check during use to assess level, as a guide toward setting cleaning/service intervals and procedures.

Line 1639
Recommend that the priming statement and guidance be extended to all DPIs.

Line 1806
The guidance should provide clarity on package insert requirements. When a delivery system includes a DPI that is packaged separately from the dosing units, the appropriate package insert should be provided with each.

Line 1854
This statement should reference studies carried out on appropriate patient groups. Not all DPIs are targeted to patients with diseased lungs.

End of comments

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